



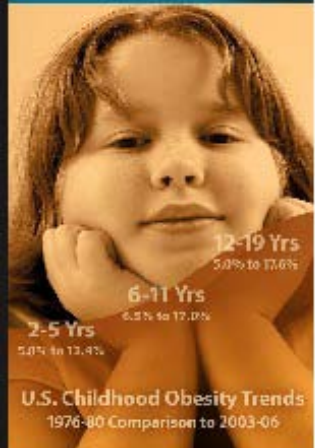
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NTP Workshop: Role of Environmental Chemicals in the Development of Diabetes and Obesity

Breakout Group on Maternal Smoking/Nicotine & Pesticides

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Deepa Rao (rapporteur)

**Crabtree Marriott Hotel
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Maternal Smoking/Nicotine + Pesticides Breakout Group Members

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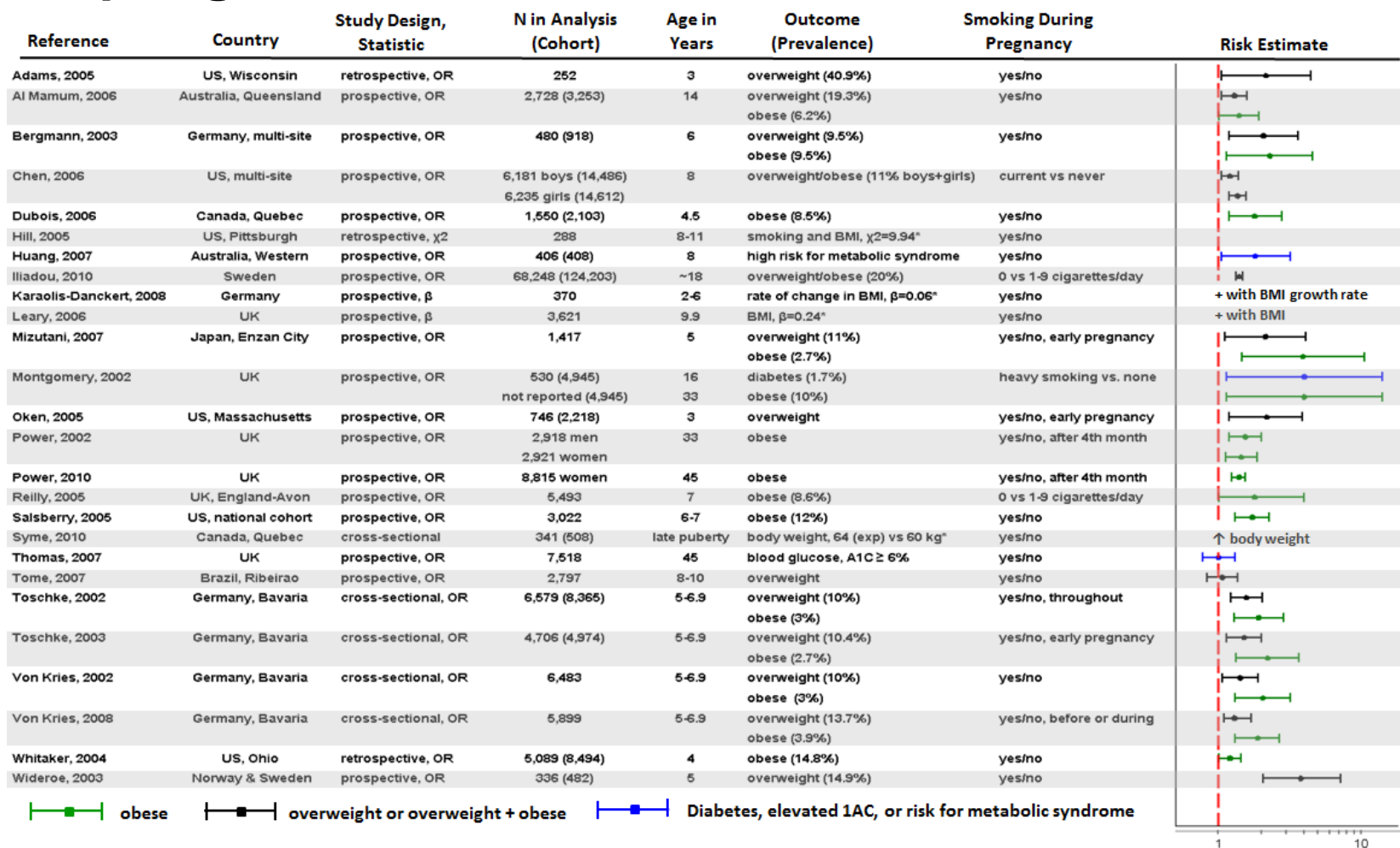
Morris White, Harvard



Maternal Smoking/Nicotine



Epidemiological data support an association between maternal smoking and increased risk of obesity in offspring





Maternal smoking and obesity/diabetes

- The data gaps in this area include:
 - Far fewer studies investigating an association between maternal smoking and risk of diabetes (T1 > T2)
 - The effects of second-hand smoke (SHS) have largely been unexplored
 - Metabolic effects of smoking and second-hand smoke exposure during other developmental stages, specifically adolescence, have not been determined.



Animal studies of developmental exposure to nicotine

- Reproduce to a large extent the changes in metabolic function seen in the offspring of children born to mothers who smoke
- Suggest biologically plausible associations between nicotine exposure and disruption of pathways important in diabetes and obesity
 - For example effects of nicotine on beta cell mass and function and to a lesser extent studies on neuropeptide expression
- However, there are a number of pathways important for these diseases (including peripheral insulin signaling, neurohumoral signaling, feeding behavior, energy balance, brain and peripheral inflammation and insulin resistance) which remain largely unexplored



Understanding the effect of smoking and SHS on diabetes and obesity risk is an important research need as this chemical exposure may exacerbate the risk of diabetes/obesity associated with exposures to other chemicals under consideration



To address data gaps in this area we suggest the following research strategy

- Identify the postnatal metabolic consequences of maternal exposure to second hand smoke in human populations
- For human data there is limited information regarding the link between nicotine exposure and diabetes or obesity. This data may available in results from NRT during pregnancy trials (developmental exposure), or (adult exposure) studies of people using snus, NRT following smoking cessation, nicotine therapeutics for non-smokers. Other data may be available from the FDA for nicotinic acetylcholine receptor agonist drugs, and putative “reduced” harm cigarettes.



Research strategy cont.

- In animal studies: explore mechanistic pathways must be explored using novel experimental paradigms including in vivo and in vitro assays to understand how smoking modulates genomic/epigenomic and molecular targets that coordinate central and peripheral nutrient homeostasis and metabolic function. Elucidating these mechanisms will also inform decisions regarding intervention strategies.
- Determine the relative contribution of other constituents of cigarette smoke. We suggest a graded step wise manner—starting with HTS type screening with relevant cell types and then in vivo alone and then in vivo in combination with nicotine.



Research strategy cont.

- Explore the hypothesis that fetal/neonatal exposure to smoking/nicotine sensitizes the offspring to adverse effects of obesogenic diets. Although perturbations in the microbiome profile have been associated with diabetes and obesity the contribution/interactions with smoking have not been explored and may also influence susceptibility to adverse diets



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Pesticides



Pesticides – Human studies

- The epidemiological data support a biologically plausible association between pesticide exposure and increased risk of diabetes and obesity in adults. However, major deficiencies in the epidemiological studies include:
 - Effects of developmental exposure have not been characterized
 - The fact that the exposures are often not well quantified (i.e., not confirmed by analytical measures)
 - The timing and duration of exposure is often not known.



To address research gaps in this area we suggest the following approach in human populations

1. Focus research effort in this field on developmental exposure in populations with documented and quantified exposures using nested longitudinal cohort design with exposure measures
 - Priority populations for these studies would have higher than typical exposure levels (i.e., agricultural and inner-city communities, pesticide applicators)
2. Refine data in adult populations using better exposure metrics
3. Focus on exposure measures and relationship to abnormal metabolic outcomes for compounds for which there is already either human or animal data pointing towards biological plausibility
4. Employ genomic based strategies (GWAS/EWAS) to further refine aforementioned longitudinal studies to identify vulnerable subpopulations



To address research gaps in this area we suggest the following approach in animal studies

1. Design animal studies to investigate developmental exposures to pesticides. Compounds can be selected using different strategies including but not limited to:
 - Those for which there is either quantified human exposure and/or the ability to measure exposure in humans.
 - Compounds chosen based on prevalence of use in the general population
 - In either case, design the animal studies to specifically focus on metabolic outcomes relevant for diabetes and/or obesity including interactions with postnatal diet



Animal studies cont.

2. Concurrently, use *in vitro* assays to determine the effects of a wider array of pesticides on functional outcomes known to be relevant to metabolic disorders (ex insulin signaling, beta cell function, brain inflammation, etc.)
3. Enhance the array of genes used in Tox21/ToxCast™ to enrich this platform for pathways relevant to metabolic disorders including those novel pathways identified from the *in vivo* animal studies and then screen pesticides (past, current and future) using Tox21/ToxCast™ with the goal of obtaining mechanistic data on the mode of action
4. Once the enhanced Tox21/ToxCast™ platform is developed, screen positive compounds from *in vivo* studies to validate that the platform is predictive of metabolic disorders. Use disparities between the Tox21/ToxCast™ platform and the *in vivo* data to refine the gene set included in Tox21/ToxCast™